REMARKS

Claims 1-32 were pending in the present application. Claims 10-20 were previously withdrawn from consideration as drawn to a non-elected invention. Claims 1 and 7 have been amended for clarity and claim 25 has been amended to clarify dependency. New claims 33-40 have been added. Support for these new claims can be found throughout the specification and in the originally filed claims. Accordingly, claims 1-9 and 21-40 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any subject matter of the claims as previously presented.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Concerning the rejection of claims under 35 U.S.C. § 112, second paragraph

Claim 25 stands rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention.

Applicants have amended claim 25 to correct dependency thereby mooting this rejection.

Withdrawal of rejection of claims under 35 U.S.C. § 112, first paragraph

Applicants acknowledge that the rejection under 35 U.S.C.§ 112, first paragraph has been withdrawn by the Examiner. The Examiner states that an adenoviral vector can be used to produce a recombinant protein *in vitro*. Applicants note that an adenoviral vector can be used to produce a recombinant protein *in vivo* as well as *in vitro,* and that bases for this rejection as articulated in the previous Office Action were addressed in the response dated July 23, 2002.

Concerning the rejection of claims under 35 U.S.C § 103(a)

Applicants note that the Examiner does not maintain the previous 35 U.S.C. § 103(a) rejection of claims 1-4 over Hayden et al., 1997 (US Patent No. 5,658,729) in view of Hutter et al., 1994 (Circulation, Vol.89, No. 1, p. 355-360) and Stege et al., (Experimental Cell Research,

Vol. 214, No. 1, p. 279-284). Applicants note that the Examiner does not maintain the 35 U.S.C. § 103(a) rejection of claims 5 and 7-9 over Hayden et al., 1997, Hutter et al., 1994, and Stege et al., 1994 as applied to claims 1-4 above, and further in view of McGrory et al., 1988 (Virology, Vol. 163, p. 614-617). Applicants acknowledge that these rejections have been withdrawn by the Examiner.

Claims 1-4, and 25-32 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mestril et al., 1994 (J. Clin. Invest., Vol. 93, p. 759-767) in view of Giordano et al., 1993 (Circulation, Vol. 88, p. I-139) and Hayden et al., 1997 (US Patent No. 5,658,729). Applicants have amended claim 25 to correct dependency. Therefore, claim 25 should fall outside this rejection.

Applicants traverse this rejection. Applicants do not agree or concede that a *prima facie* case of obviousness has been established and submit that the invention is non-obvious in view of the cited references. In order to establish a *prima facie* case of obviousness, there has to be, *inter alia*, some motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine reference teachings. Applicants submit that the references cited do not provide motivation for combining the references or modifying the art cited and, even if combined, the combination of references does not produce the claimed invention.

The presently claimed invention recites a replication-deficient recombinant adenoviral vector comprising a stress related factor which is a heat shock protein, methods of producing a replication-deficient adenoviral vector, host cells, viral particles, and compositions comprising said particles and host cells. As correctly stated by the Examiner, Mestril et al. have no teachings or suggestions whatsoever regarding the use of any adenoviral vector, much less a replication-deficient recombinant adenoviral vector, or the use of a CMV or myocyte-specific promoter, or adenoviral particles or compositions comprising adenoviral vectors. Mestril et al. have no teachings or suggestions whatsoever regarding methods of making replication-deficient recombinant adenoviral vectors comprising a stress related factor. Mestril et al. generated stably

transfected cell lines overexpressing the human-inducible HSP70, wherein the HSP70 gene is under the transcriptional control of SV40 enhancer-TK promoter. See Mestril et al. page 759. The Examiner states that Giordano et al. teach that recombinant replication-deficient adenoviral vector is an effective vector for delivery of foreign or endogenous genes to mycardium and endothelium. Giordano et al. have no teachings whatsoever regarding replication-deficient recombinant adenoviral vectors (or viral particles) comprising a stress related factor which is a heat shock protein, methods of producing such replication-deficient adenoviral vector, or compositions comprising such vectors. Giordano et al., which is an abstract, have no teachings whatsoever about stress related factors including heat shock protein and suggest methods for transfection without the need for constructing recombinant AdV. See Giordano et al. last sentence. Hayden et al. relate, in part, to identification of a single point mutation in the human lipoprotein lipase gene (LPL) that is seen with increased frequency in patients with coronary artery disease and, in part, to gene therapy to introduce functional LPL into a patient subject to a defect in LPL. As previously concluded by the Examiner, there is no teaching or suggestion whatsoever in Hayden et al. of a recombinant, replication-deficient adenoviral vector (or viral particles) expressing a heat shock protein, host cells or compositions comprising such vectors or methods of making such vectors.

Furthermore, there is no suggestion whatsoever in any of the references to combine them. There is no suggestion in Mestril et al., which have no suggestions whatsoever of the use of a replication deficient adenoviral vector, to combine with Giordano et al., which have no suggestions about the use of stress related proteins including heat shock proteins and instead and in contrast to the present invention suggest the use of methods for transfection without the need for constructing recombinant adenovirus (AdV), and to combine with Hayden et al., which relate to a single point mutation in LPL and gene therapy to introduce functional LPL into a patient subject to a defect in LPL. That the Examiner would combine these references to allege non-obviousness is the result of the impermissible use of hindsight reconstruction.

Applicants remind the Examiner of MPEP 707.02 which states that the shortest path to a final disposition of an application is by finding the best references on the first search and carefully applying them. The Examiner in the first Office Action applied and subsequently withdrew Hayden et al., 1997 (US Patent No. 5,658,729) in view of Hutter et al., 1994 (Circulation, Vol.89, No. 1, p. 355-360) and Stege et al. In the instant second, non-final Office Action, the Examiner applies a new Section 103 rejection based on new art, that is, Mestril et al., which have no teachings whatsoever regarding the use of adenoviral vectors and Giordano et al., which have no suggestions of the use of stress related proteins including heat shock proteins and suggest the use of methods for transfection without the need for constructing recombinant AdV in combination with Hayden et al which relate to LPL point mutations. The claimed invention is non-obvious over the cited art. Applicants respectfully request withdrawal of the Section 103(a) rejection of claims.

Applicants respectfully request that pursuant to MPEP 707.02, this application be personally checked on by the supervisory patent examiner since it is potentially up for a third Office Action.

B. Claims 1, 5, 7-9 and 21-24 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mestril et al., 1994 (J. Clin. Invest., Vol. 93, p. 759-767) in view of et al., 1993 (Circulation, Vol. 88, p. I-139) and Hayden et al., 1997 (US Patent No. 5,658,729) as applied to claims 1-4 and 25-32 above, and further in view of McGrory et al., 1988 (Virology, Vol. 163, p. 614-617).

Applicants traverse this rejection of claims. Applicants do not agree or concede that a *prima facie* case of obviousness has been established and submit that the invention is non-obvious in view of the cited references. There is no motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine reference teachings. Even if the references are combined, the combination of references does not produce the claimed invention. The deficiencies of Mestril et al., Giordano et al., and Hayden et al. are discussed above. The addition of McGrory et al. does

not cure the deficiencies of the primary references. McGrory et al. relate to methods of rescuing adenovirus E1 mutants into infectious virions. See McGrory et al. page 616. There is no teaching or suggestion whatsoever in McGrory et al. of replication-deficient adenoviral vectors (or particles) comprising a transgene coding for a stress factor which is a heat shock protein, host cells or compositions comprising or methods of making. Furthermore, there is no suggestion in any of the references to combine them and if combined, one of skill in the art would not arrive at the presently claim invention. That the Examiner would combine these references to arrive at this obviousness rejection is the result of the impermissible use of hindsight reconstruction. Therefore, Applicants respectfully request withdrawal of this Section 103 rejection.

Concerning the objection of claims

Claim 6 has been objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants acknowledge the Examiner's indication of allowable subject matter. Applicants believe that claim 6 is allowable as written since the rejected base claim is non-obvious over the cited art.

Rejoinder of methods claims

Applicants request rejoinder of methods claims to the extent they incorporate all the limitations of allowed composition claims. In re Ochiai.

CONCLUSION

Applicants have made a sincere effort to overcome the rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 220002057202.

Respectfully submitted,

Dated: Feb 19, 2003 By: _____

Debra J. Glarster
Registration No. 33,888

Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018
Telephone: (650) 813-5725
Facsimile: (650) 494-0792

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend claims 1, 7 and 25, as follows:

1. (Thrice amended) An isolated recombinant, replication-deficient adenoviral vector, said vector comprising:

an adenoviral sequence from which the E1A/E1B genes have been deleted;

a transgene coding for a stress related factor which is a heat shock protein; and

a promoter operably linked to said transgene[, wherein expression of the transgene is controlled by said promoter].

7. (Once Amended) The method of claim 5, wherein said identification comprises the steps of:

monitoring transfected cells for evidence of cytopathic effect;

treating the cell supernatant from cell cultures showing a cytopathic effect with proteinase K, followed by phenol/chloroform extraction and ethanol precipitation to isolate viral DNA;

identifying cells producing recombinant vectors [with PCR using primers complementary to the CMV promoter and primers complementary to adenoviral sequences]; and

purifying recombinant vectors using two rounds of plaque purification.

25. (Once Amended) The method of claim 21 wherein said adenoviral vector is a human adenoviral vector.

New claims 33-40 have been added.